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ORIGINAL REPORT

Evidence for Cure by Adjuvant Therapy in Colon Cancer: Observations Based on Individual Patient Data From 20,898 Patients on 18 Randomized Trials

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Limited data are available on the time course of treatment failures (recurrence and/or death), the nature and duration of adjuvant treatment benefit, and long-term recurrence rates in patients with resected stage II and III colon cancer.

Methods
The data set assembled by the Adjuvant Colon Cancer Endpoints Group, a collection of individual patient data from 18 trials and more than 20,800 patients testing fluorouracil-based adjuvant therapy in patients with stage II or III colon cancer, was analyzed.

Results
A significant overall survival (OS) benefit of adjuvant therapy was consistent over the 8-year follow-up period. The risk of recurrence in patients treated with adjuvant chemotherapy never exceeds that of control patients, signifying that adjuvant therapy cures some patients, as opposed to delaying recurrence. After 5 years, recurrence rates were less than 1.5% per year, and after 8 years, they were less than 0.5% per year. Significant disease-free survival (DFS) benefit from adjuvant chemotherapy was observed in the first 2 years. After 2 years, DFS rates in treated and control patients were not significantly different, and after 4 years, no trend toward benefit was demonstrated. This benefit was primarily driven by patients with stage III disease.

Conclusion
Adjuvant chemotherapy provides significant DFS benefit, primarily by reducing the recurrence rate, within the first 2 years of adjuvant therapy with some benefit in years 3 to 4, translating into long-term OS benefit. This reflects the curative role of chemotherapy in the adjuvant setting. After 5 years, recurrence rates in patients treated on clinical trials are low, and after 8 years, they are minimal; thus, long-term follow-up for recurrence is of little value.

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INTRODUCTION

Approximately 145,000 new patients with colorectal cancer are diagnosed annually in the United States. When diagnosed at a stage when curative surgical resection is possible, fluorouracil (FU)-based adjuvant chemotherapy for colon cancer has repeatedly been shown to improve patient overall survival (OS). FU with leucovorin became standard of care for patients with stage III and selected stage II colon cancer in the early 1990s[1-4] and provided the basis for the addition of oxaliplatin, which has been demonstrated to further improve disease-free survival (DFS) and OS in stage III patients.[5,6] Although adjuvant chemotherapy is routinely administered for only a limited duration of time (usually 6 months), it apparently leads to long-term benefits in outcome, usually measured in terms of 3- and 5-year rates of OS or DFS.

Graphical presentations of survival or recurrence data from clinical trials, typically presented using Kaplan-Meier plots, convey information regarding the absolute rate of recurrence, DFS, and OS at any given time point. However, these plots do not readily convey the risk of an event at a specific time point, and a separation in survival curves does not convey the interpretation of an early advantage that is maintained over time as opposed to a continued difference in the relative risk of an event. Therefore, the clinical demonstration of actual cure of patients by adjuvant therapy is poorly understood, both in colorectal cancer and in

other solid tumors. More detailed information on the time course of recurrence, such as both short- and long-term year-by-year failure rates stratified by untreated and treated patients, may assist in patient counseling and in determining follow-up recommendations. Furthermore, such analyses also provide information on the long-standing question of whether adjuvant therapy in colon cancer completely eradicates tumor cells, thus allowing for higher cure rates, or whether treatment only delays tumor recurrence. On the basis of individual patient data from 20,898 patients randomly assigned on 18 trials of adjuvant therapy for colon cancer, we studied the time course of treatment failure and long-term recurrence rates.

METHODS

The data set assembled by the Adjuvant Colon Cancer Endpoints (ACCENT) Group was used for all analyses.[7] As previously described, ACCENT identified and obtained individual patient data from 18 phase III adjuvant trials in colon primary tumors conducted from 1978 to 1999. A total of 20,898 patients and 43 distinct treatment arms (34 active treatment arms and nine surgery-only arms) are included in the ACCENT database. Table 1 and Appendix Table A1 (online only) list the details regarding the trials and patient characteristics, respectively.

This analysis focused on continuous time estimation of the hazard rate (risk of recurrence or death) by treatment over time, as well as the continuous time estimation of the hazard ratio (HR) comparing FU-based treatment with control. The continuous time estimation of these rates and ratios allows the risk of an event (for hazard rates) and benefit of treatment (for HRs) to vary over time. This is in contrast to the usual estimated HR from a Cox proportional hazards regression, which assumes that the HR between the two treatment arms has a single value that is constant over time. Hazard rates over time were estimated by the method of Müller and Wang.[8] HRs, with 95% pointwise CIs, were estimated using the method of Gilbert et al.[9] The end points of OS, DFS, and time to recurrence (TTR) were considered. OS is defined as time to death from any cause. DFS is defined as the time to recurrence or death, whichever occurs first. TTR is defined as the time to disease recurrence, where deaths without recurrence were censored at the time of death. Recurrence was defined only by a reappearance of primary colon cancer; second primary colon cancers or other noncolon cancers were not classified as recurrences. Because the definitions of these terms (DFS and TTR) were not consistent across all included trials, the definitions here may differ from those used in the original trial. The analysis of the overall treatment benefit was performed with a log-rank test comparing treatment with control, stratified by the original trial.

Analyses comparing FU-based treatment with control were limited to the nine trials with a no-treatment control arm (n = 4,922; National Surgical Adjuvant Breast and Bowel Project [NSABP] C-01 and C-02, North Central Cancer Treatment Group [NCCTG] 784852, Fédération Francophone de Cancérologie Digestive, Intergroup 0035, Interdisciplinary Group for Cancer Care Evaluation, NCCTG 874651, Siena, and National Cancer Institute of Canada trials in Table 1). Because of inconsistent long-term follow-up for the hazard rate and HR analyses, all patients were censored at 8 years for analysis of treatment benefit. Long-term event rates were estimated using data from all trials where the median follow-up time for living patients exceeded 9 years (eight trials, n = 11,615; NCCTG 784852, Intergroup 0035, Intergroup 0089, and NSABP C-01, C-02, C-03, C-04, and C-05 trials in Table 1).

Table 1. Trials Included

Trial	Accrual Period	Treatment Arms	No. of Patients
NSABP C-01	1977-1983	Control *v* MOF	724
NCCTG 784852	1978-1984	Control *v* FU/LEV	247
FFCD	1982-1990	Control *v* FU/LV	239
NSABP C-02	1984-1988	Control *v* PVI FU	896
INT 0035	1984-1987	Control *v* FU/LEV	926
Siena	1985-1990	Control *v* FU/LV	256
NCIC	1987-1992	Control *v* FU/LV	359
NSABP C-03	1987-1989	MOF *v* FU/LV	1,042
NCCTG 874651	1988-1989	Control *v* FU/LV	408
GIVIO	1989-1992	Control *v* FU/LV	867
NCCTG 894651	1989-1991	FU/LV ± LEV for 6 or 12 months	915
NSABP C-04	1989-1990	FU/LEV *v* FU/LV *v* FU/LV/LEV	2,083
INT 0089	1990-1992	FU/LEV *v* FU/LV (HD or LD) *v* FU/LV/LEV	3,561
NSABP C-05	1991-1994	FU/LV *v* FU/LV + IFN	2,136
NCCTG 914653	1993-1998	FU/LV + HD or standard LEV	878
SWOG 9415	1994-1999	Bolus *v* infusional FU/LEV/LV	939
QUASAR	1994-1997	FU/LV (HD or LD) ± LEV	3,517
GERCOR	1996-1999	Bolus *v* infusional FU/LV	905
Total			20,898

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; MOF, semustine, vincristine, and fluorouracil; NCCTG, North Central Cancer Treatment Group; FU, fluorouracil; LEV, levamisole; FFCD, Fédération Francophone de Cancérologie Digestive; LV, leucovorin; PVI, protracted venous infusion; INT, Intergroup; NCIC, National Cancer Institute of Canada; GIVIO, Interdisciplinary Group for Cancer Care Evaluation; HD, high dose; LD, low dose; IFN, interferon alfa-2a; SWOG, Southwest Oncology Group; QUASAR, Quick and Simple and Reliable Collaborative Group; GERCOR, French Multidisciplinary Clinical Research Group.

RESULTS

Hazard Rates

Of the 20,898 patients, 35% experienced recurrence and 38% died in the initial 8-year follow-up period. Sixty-six percent of patients had stage III disease, and 33% had stage II disease. When the analyses were restricted to the 4,922 patients on trials in which they were randomly assigned to adjuvant treatment versus surgery alone, 1,670 patients (34%) experienced recurrence, and 1,910 patients (39%) died. Traditional Kaplan-Meier plots of OS by stage for patients randomly assigned to treatment versus control are presented in Figure 1.

To provide additional insight into the time-related nature of adjuvant therapy benefit, hazard rates over time for OS, DFS, and TTR by treatment group are shown in Figure 2. For both treated and untreated patients, the risk of death from any cause (Fig 2A) peaks at approximately 2 years after surgery and gradually declines over the 8-year estimation period. For the DFS and TTR end points (Figs 2B and 2C), in untreated patients, the risk of an event clearly is highest in the year after surgery, with a rapid reduction until approximately year 4. The failure rate in treated patients is low initially and then increases in years 1 to 3, only to recede close to the rate in untreated patients by year 4. The DFS curves (Fig 2B) remain slightly separated in years 4 to 8 between treatment and control, whereas the TTR curves (Fig 2C) are virtually superimposable in that time period. For none of the end points does the failure rate for treated patients ever exceed that of the untreated patients during the 8-year follow-up period.

These patterns of treatment failure over time are substantially different for stage II and stage III patients (Fig 3). In stage III patients, the absolute risk of a DFS event is greater than for stage II patients in the first 4 years of follow-up, becoming similar after years 5 to 6 as the DFS end point becomes dominated by death events. In addition, the relative benefit of treatment is considerably larger in stage III patients, with a longer duration of benefit. In stage II patients, the modest early

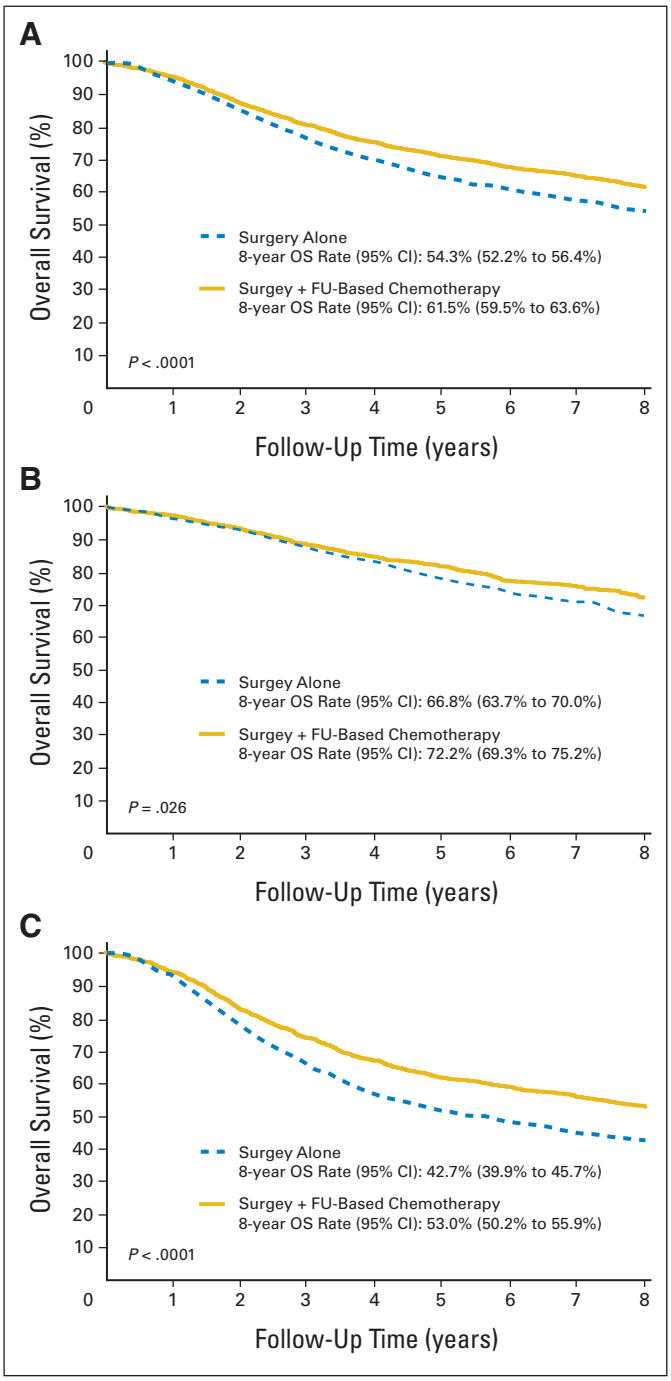

Fig 1. Kaplan-Meier plots of overall survival (OS) in treatment arm versus control arm for (A) all patients, (B) stage II patients, and (C) stage III patients. FU, fluorouracil.

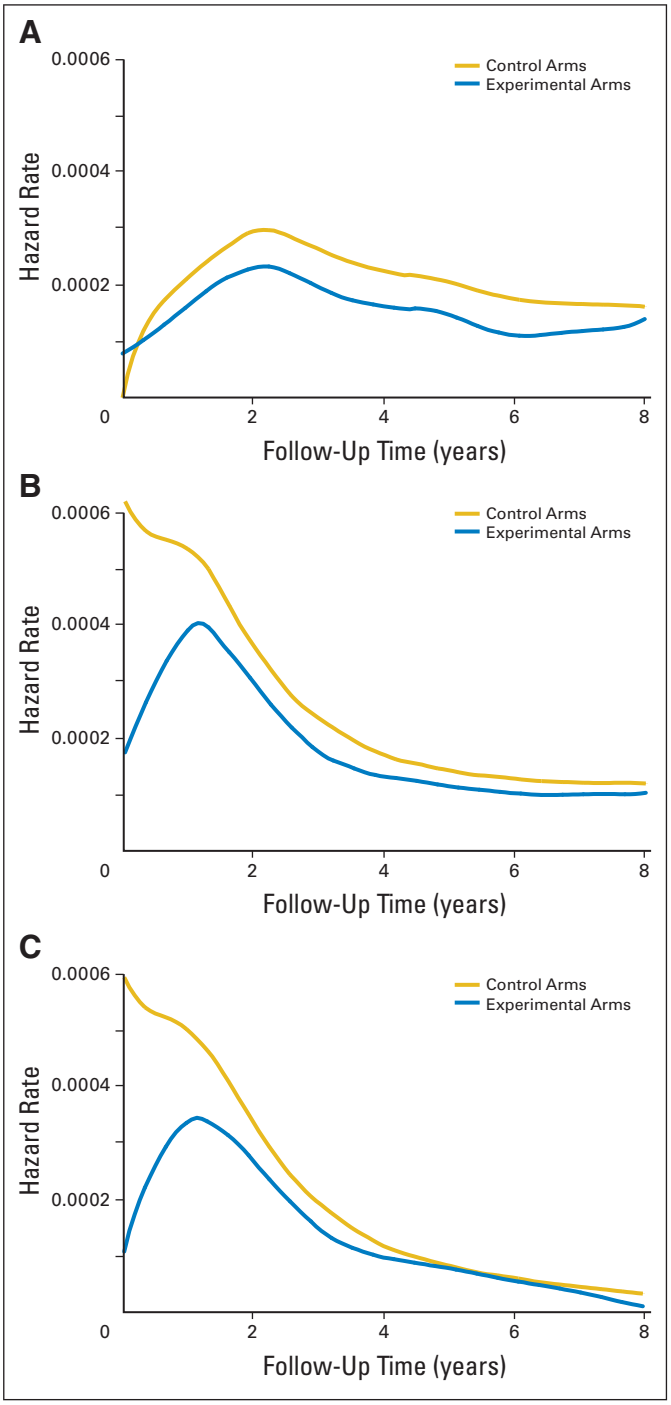

Fig 2. Hazard rates by time from random assignment and treatment arm. Plots of the hazard rate for (A) overall survival, (B) disease-free survival, and (C) time to recurrence by arm (treatment and control) over the 8-year follow-up period. The *y* axis plots the risk of recurrence on a daily scale; thus, for example, the value 0.0002 represents an annualized 7.3% risk of an event (0.0002 × 365 = 0.073).

benefit in reducing DFS events is entirely absent after 2 to 3 years, whereas in stage III patients, it remains for at least 4 years.

HRs (with 95% pointwise CIs) comparing patients on the treatment versus control arms of trials, plotted on the logarithmic scale, for the OS, DFS, and TTR end points are shown in Figure 4. Figure 4A demonstrates that the addition of adjuvant therapy provides a consistent and durable beneficial effect on OS over the follow-up period, with an estimated log-HR of −0.30 (HR = 0.74) that is consistent over time. In contrast, in Figures 4B and 4C, there is a substantial benefit of adjuvant therapy in reducing the risk of a DFS or recurrence event the first 1 to 2 years after resection (estimated log-HR in the range of −0.50; HR = 0.61) that diminishes over time and becomes nonsignificant (based on 95% pointwise CIs) after year 4, signifying that the DFS and recurrence rates are statistically similar between treatment and control arms after 4 years.

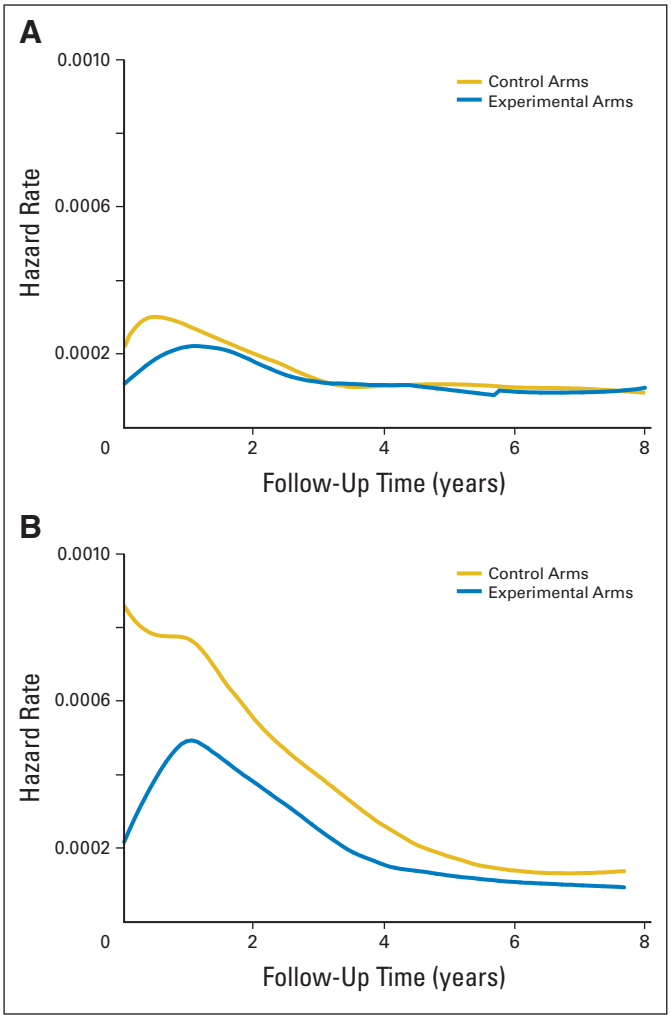

Fig 3. Disease-free survival hazard rates by time from random assignment and treatment arm in (A) stage II patients and (B) stage III patients.

Long-Term Recurrence Rates

Of the 20,898 patients, 11,615 were enrolled onto trials where the median follow-up time exceeds 9 years. Figure 5 presents the recurrence rates, by 6-month intervals, to 15 years of follow-up. After 5 years, the recurrence rate by year never exceeds 1.5%, and after 8 years, it never exceeds 0.5%.

DISCUSSION

These results illustrate the following three important concepts for the management of early colon cancer: adjuvant FU-based treatment actually eradicates colon cancer cells, thereby curing patients; late relapses can occur, but after 8 years, the notion of cure is appropriate; and most relapses occur in the first 2 years after surgery. These concepts are relevant to our understanding of tumor biology, clinical practice, and future clinical trial design.

A previous pooled analysis of FU-based adjuvant colon cancer trials demonstrated a highly statistically significant 11% absolute improvement in 5-year freedom from recurrence as a result of FU-based adjuvant therapy.[10] In the current analysis, including additional

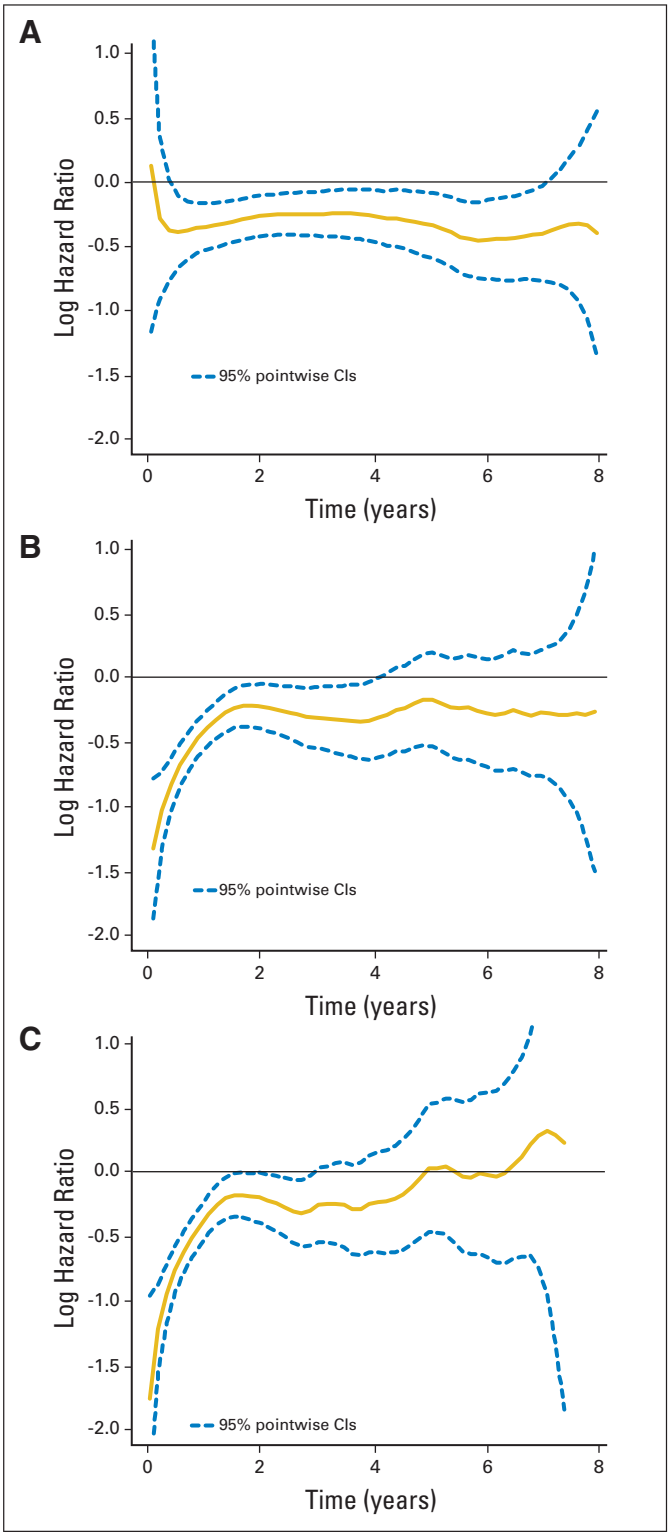

Fig 4. Continuous time estimate of the log-hazard ratios for (A) overall survival, (B) disease-free survival, and (C) time to recurrence comparing treatment arm with control arm over the 8-year follow-up period, with 95% pointwise CIs. Values less than 0 indicate a benefit from treatment. For example, a value of −0.50 for the log-hazard ratio indicates a hazard ratio of 0.61 comparing treatment with control at that time point ($e^{-0.50} = 0.61$), that is, a 39% reduction in the risk of an event.

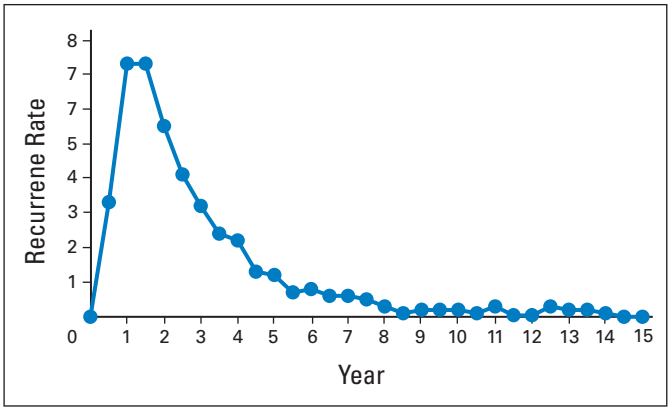

Fig 5. Risk of recurrence in each 6-month interval after random assignment among patients remaining recurrence free at the start of each interval, by time.

patients, overall adjuvant therapy resulted in a 7% improvement in 8-year OS rate (5% in stage II patients and 10% in stage III patients). Because the current analysis included two trials without FU/leucovorin or FU/levamisole chemotherapy arms, these survival improvements likely underestimate the true survival benefit of FU and leucovorin therapy. Importantly, in the current analysis, the hazard rates of OS, DFS, and TTR in treated patients never exceed the corresponding rates in untreated patients, at least in the 8-year follow-up period reported here. The lack of any crossing of the hazard rate curves indicates that adjuvant therapy is a curative intervention by intent. If therapy simply delayed, as opposed to prevented, recurrences, we would expect the TTR hazard rate for treated patients to eventually exceed the rate in the untreated patients. Instead, the hazard rates separate between 6 months and 2 years from random assignment, a time perfectly compatible with the effect of chemotherapy. In addition, at least in the 8-year follow-up period, the fact that the OS hazard rate in the treated patients remains lower than in the untreated patients supports the lack of a meaningful detrimental long-term effect of FU-based chemotherapy, as measured by OS.

It may be considered surprising that single-agent FU-based chemotherapy, which produces only a modest benefit in the advanced disease setting (consistent response rate of 15%, progression-free survival time of 4 month, and median survival time of 11 to 12 months), ultimately leads to an approximate 10% cure rate in the pooled population of high-risk stage II and III patients included in these trials when used in the adjuvant setting. Biologic plausibility may tempt us to extend this paradigm to combinations of newer cytotoxic drugs (oxaliplatin and irinotecan) or to targeted agents such as bevacizumab or cetuximab, and beyond (biologics). However, great caution must be exercised. The results to date in the adjuvant setting demonstrate that the paradigm of predicting activity in the adjuvant setting based on studies in advanced disease works for combining oxaliplatin with FU and leucovorin. On the basis of the results of the Adjuvant Treatment of Colon Cancer (MOSAIC) trial,[5] the 20% improvement in response rate and 3 months of additional PFS time afforded by infusional FU, leucovorin, and oxaliplatin compared with FU and leucovorin in the advanced setting translate into an approximately additional 7% gain in 3-year DFS in the adjuvant setting for stage III patients. Recently, this early DFS improvement has translated into a longer-term OS benefit after 6 years of follow-up.[11] Our findings suggest that this OS benefit will be maintained and may even grow over time, because few late recurrences are to be expected. However, although irinotecan combined with FU and leucovorin produces a benefit similar to oxaliplatin with FU and leucovorin in the advanced disease setting, this benefit has failed to translate into any significant benefit when irinotecan is added to adjuvant FU and leucovorin.[12,13] Therefore, the empirical data demonstrate that the paradigm that efficacy in advanced disease leads to efficacy in the adjuvant setting is indeed agent dependent. Extending this concept to other tumors, the positive early experience with adjuvant trastuzumab in breast cancer[14] and adjuvant imatinib in GI stromal cell tumors[15] provides hope that this paradigm will hold for biologic agents as well. More specifically, this concept is relevant to the adjuvant therapy of colon cancer because clinical trials using oxaliplatin with FU and leucovorin plus either bevacizumab or cetuximab have completed or are about to complete accrual or are ongoing (NSABP C-08; AVANT; E5202; Quick and Simple and Reliable Collaborative Group-2: bevacizumab; NCCTG N0147; and PETACC-8: cetuximab).[16] However, the unique mechanism of action of these biologic agents may require additional years of follow-up before conclusions regarding a relapse-delaying versus a curative effect of these complex treatments can be reliably ascertained. It is possible that biologic agents such as angiogenesis inhibitors might delay the occurrence of detectable metastatic disease without actually eradicating tumor cells, thereby leading to improvements in early DFS without affecting long-term OS.[16] Regardless of the agent's mechanism of action, as survival after recurrence is extended by effective therapy for metastatic disease, longer term follow-up is likely to be required to establish a long-term survival benefit.[17]

Our results also provide valuable data to clinical practice regarding the long-term risk of recurrence in patients with colon cancer who undergo curative resection. We have previously demonstrated that 80% of colon cancer patients who experienced recurrence in the first 8 years after surgery do so in the first 3 years.[7] These new results not only confirm this finding, but also demonstrate that the risk of recurrence continues to be low for up to 15 years of follow-up. On the basis of this information, from a clinical trials perspective, there is little value in mandating follow-up for recurrence beyond 5 years in future adjuvant colon cancer trials. From a clinical perspective, once a patient has been recurrence free for 5 years from surgery, continued medical care can focus on other issues beyond the patient's prior colon cancer such as long-term adverse effects of the adjuvant therapy or secondary cancers, which are issues that may be more clinically relevant and prevalent in these patients.

Finally, these analyses clearly demonstrate that in untreated patients, the risk of recurrence is dominated by the early postsurgical period, in particular the first 2 years. The clear major benefit of adjuvant therapy is to significantly and meaningfully reduce this risk of early recurrence by approximately 40%. From years 2 to 4, the TTR and DFS rates remain slightly reduced in patients receiving adjuvant therapy; however, the magnitude of benefit is clearly less than in the early time period. Careful follow-up in the first 5 years for recurrence is critical because an increasing number of patients found to have early recurrence have the potential for cure by salvage surgery.[18,19] The OS hazard rate and HR plots (Figs 2A and 3A) indicate that this short-term reduction in risk of recurrence translates into long-term advantages in OS. As previously discussed,[20] this early effect of adjuvant chemotherapy could further reduce the required time to obtain relevant information from clinical trials in the adjuvant setting.

Continued analyses of large datasets, such as ACCENT, provide valuable information that is useful to statisticians (eg, the adequacy of statistical models), clinical trialists (eg, event rates over time), and practicing oncologists (eg, surveillance patterns and prediction of cure rates). The ACCENT group will continue to seek to include data from all large randomized adjuvant colon cancer clinical trials to update these findings from single-agent FU adjuvant studies with data from current and next-generation treatment regimens.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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